REMARKS

Claims 14-20 were pending in this application. Claims 14 and 15 have been amended. Thus, as a result of the foregoing amendment, Claims 14-20 are pending. Reconsideration of the pending claims is respectfully requested.

The Examiner has objected to the incorrect use of trademarks in the present application, and has requested correction of the trademarks to reflect their proprietary nature. As such, the trademarks have been capitalized and noted accordingly. Furthermore, Applicants have provided herein a copy of a printout from the manufacturers website, noting the correct usage of GAMMABIND™ PLUS SEPHAROSE™ . The specification has been amended accordingly to reflect this correction.

The Examiner has rejected claims 14-20 under 35 U.S.C. 112, first paragraph, for lack of written description. The Examiner has alleged that the specification discloses that the hybrid proteins of the invention have the antigen binding capabilities of an antibody fragment and the longevity of serum albumin in vivo. However, the Examiner alleges that the specification does not disclose any working examples of fragments of albumin coupled to antibody fragments. Applicant(s) have traversed the Examiner's rejection and have amended the claims to delete the phrase "or a fragment thereof", thus obviating the Examiner's rejection.

The Examiner has rejected claims 14-20 under 35 U.S.C. 112, first paragraph for lack of enablement. Applicant(s) have traversed the Examiner's rejection and have amended the claims to delete the phrase "or a fragment thereof", thus obviating the Examiner's rejection.

Claims 14-20 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Applicant(s) have traversed the Examiner's rejection of claim 14 for recitation of the phrase "or a fragment thereof" and have amended claim 14 to delete this phrase, thus obviating the Examiner's rejection. Furthermore, the Examiner alleges that claim 15 is indefinite in the recitation of "around 10A to around 20A in length" because it is not clear what the metes and bounds of "A" are. Applicant(s) have traversed the Examiner's rejection and have amended the claim to read as "from around 10Å to around 20Å in length". The support for the amendment can be found in the specification on page 12, lines 13-14.

Claims 14-20 are rejected under 35 U.S.C. § 103(a), as being obvious over U.S. patent No. 6,350,431 in view of Peters (IDS reference "AT") and the known facts disclosed in the specification on page 27, lines 9-13. Furthermore, claims 14, 15 and 17-20 were rejected under 35 U.S.C. §

103(a), as being obvious over U.S. patent No. 4,751,286 in view of U.S. patent No. 4,749,570, Peters (IDS reference "AT") and the known facts disclosed in the specification on page 27, lines 9-13. Applicant(s) have respectfully traversed the Examiner's rejection and have provided evidence for non-obviousness, as shown below.

Priority Entitlement

The Examiner alleges that for the purpose of prior art rejections, the filing date of the instant claims 15 and 17-20 are deemed to be the filing date of the PCT application PCT/GB99/03747, ie. 11/10/99, as the 9824632.5 application does not support the claimed limitations of the instant application. In particular, the Examiner alleges that the limitation "wherein the bridging molecule is from around 10 Å to around 20 Å in length" is not disclosed in the 9824632.5 application.

Applicants respectfully traverse the Examiner's rejection of the priority date for the reasons cited herein and provide support for the limitation noted above in GB application No. 9824632.5. In particular, support for claim 15 and specifically the phrase "wherein the bridging molecule is from around 10 Å to around 20 Å in length" can be found on page 12, lines 5-6 of the priority document. Support for claims 17 and 18 can be found on page 11, lines 28-31 of the priority document. Furthermore, support for claim 19 can be found on page 9, lines 4-5 of the priority document. Moreover, support for claim 20 can be found on page 12, lines 29-33 of the priority document. Applicants respectfully request reconsideration of the earlier priority date for the reasons and support noted above.

Claim Rejections under 35 U.S.C. §112

Rejections Under 35 USC § 112, first paragraph

The Examiner has rejected claims 14-20 under 35 U.S.C. 112, first paragraph, for lack of written description. The Examiner alleges that the specification discloses that the hybrid proteins of the invention have the antigen binding capabilities of an antibody fragment and the longevity of serum albumin in vivo. However, the Examiner alleges that the specification does not disclose any working examples of fragments of albumin coupled to antibody fragments. Applicant(s) have traversed the Examiner's rejection and have amended the claims to delete the phrase "or a fragment

thereof", thus obviating the Examiner's rejection. Withdrawal of the rejection is respectfully requested.

The Examiner has rejected claims 14-20 under 35 U.S.C. 112, first paragraph for lack of enablement. The Examiner alleges that the specification does not enable the breadth of the claimed invention because the specification does not disclose how to make or use the hybrid protein/composition thereof, comprising one antigen binding antibody fragment covalently linked to a fragment of albumin, including at position 34 of albumin. The Examiner alleges that the specification does not enable the breadth of the claimed invention because the claims encompass hybrids of undisclosed structure. Applicant(s) have traversed the Examiner's rejection and have amended the claims to delete the phrase "or a fragment thereof", thus obviating the Examiner's rejection. Withdrawal of the rejection is respectfully requested.

Rejections Under 35 USC § 112, second paragraph

Claims 14-20 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner alleges that claim 14 is indefinite because there is no recitation of "or fragment thereof" after the second occurrence of albumin in line 2. Applicant(s) have traversed the Examiner's rejection and have amended claim 14 to delete the phrase "or a fragment thereof", thus obviating the Examiner's rejection. Furthermore, the Examiner alleges that claim 15 is indefinite in the recitation of "around 10A to around 20A in length" because it is not clear what the metes and bounds of "A" are. Applicant(s) have traversed the Examiner's rejection and have amended the claim to read on angstroms, that is, "from around 10Å to around 20Å in length". The support for the amendment can be found in the specification on page 12, lines 13-14. Withdrawal of the rejection is respectfully requested.

Claim Rejections under 35 U.S.C. §103(a)

Claims 14-20 are rejected under 35 U.S.C. § 103(a), as being obvious over U.S. patent No. 6,350,431 in view of Peters (IDS reference "AT") and the known facts disclosed in the specification on page 27, lines 9-13. The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under § 103 requires a determination of the scope and content

of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 US 1 (1966). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion that the combination be made. In re Stencel, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987). Applicants respectfully traverse the Examiner's rejection for the following reasons.

U.S. patent No. 6,350,431 reference as a whole. U.S. patent number 6,350,431 describes compounds useful as contrast agents in light imaging procedures having a polymeric structure with repeat units containing chromophores and polyalkylene oxide moieties connected by linking groups. One embodiment of this patent is an immunoreagent comprising a metal radionuclide ion in which a chelating agent present in the linking group of the polymer is complexed with a metal radionuclide ion and an immunoreactive group is attached to this polymer through a linking group. This patent lists a large number of linking groups that may be used within the polymer and to attach targeting groups to the polymer. Hexylene and albumin are therefore only two linkers out of a list of many possibilities.

The analysis under § 103(a). U.S. Patent No. 6,350, 431 does not suggest that there is any particular advantage associated with using albumin or hexylene as linkers over any of the other numerous linkers cited. Therefore, U.S. Patent No. 6,350, 431 provides no motivation to select either or both of these linkers alone or in combination in the same immunoreagent. In particular, U.S. Patent No. 6,350, 431 provides no motivation to use a hexylene linker to connect an immunoreactive group to an albumin linker.

The Examiner considers that the skilled person would have been motivated to attach a bridging molecule from the immunoreactive group to position 34 of the albumin in order to retain the native structure of the albumin. However, nowhere in U.S. Patent No. 6,350, 431 is it suggested that in order for albumin to function as a linker it should retain its native structure. The skilled person in creating the immunoreagent of U.S. Patent No. 6,350, 431 would have been solely concerned with

utilizing the best linker to link components of the immunoreagent together. Each linker in U.S. Patent No. 6,350, 431 is attached to **two** or more other components of the immunoreagent. Even if a skilled artisan had selected albumin as a linker, he would not have been concerned with retaining its native structure in order to use it as a linker to connect two or mopre components of the immunoreagent. As a result, there would have been no motivation to use position 34 or to consider the Peters reference.

The Examiner asserts that the linking molecules disclosed in U.S. Patent No. 6,350, 431 range from around 10Å to around 20Å in length. Upon review of U.S. Patent No. 6,350, 431, Applicants were unable to find explicit disclosure to this effect, nor could they find any disclosure that this length would be desirable to prevent unwanted albumin homodimer formation or to enable an antibody fragment to retain its full binding ability, as disclosed in the Applicants' current invention.

Accordingly, Applicants assert that claims 14-20 are not obvious in view of U.S. Patent No. 6,350, 431, Peters and the facts as disclosed in the specification. Withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

Furthermore, claims 14, 15 and 17-20 were rejected under 35 U.S.C. § 103(a), as being obvious over U.S. patent No. 4,751,286 in view of U.S. patent No. 4,749,570, Peters (IDS reference "AT") and the known facts disclosed in the specification on page 27, lines 9-13. Applicant(s) have respectfully traversed the Examiner's rejection and have provided evidence for non-obviousness, as shown below.

U.S. Patent No. 4,751,286 reference as a whole This patent discloses linking a monoclonal antibody to a drug, label or dye. The antibody conjugate is a whole IgG, not an antibody fragment. A drug, label or dye is attached to the whole IgG molecule.

The analysis under § 103(a). As noted by the Examiner, U.S. Patent No. 4,751,286 does not disclose any features of Applicants' invention. For example, U.S. Patent No. 4,751,286 does not disclose the possibility of using antibody fragments. Furthermore, the use of antibody fragments would contradict

the rationale for using whole IgG (column 5, line 55), since whole IgG was chosen because it 1) has been shown to have a limited number of accessible disulfide bonds and 2) the disulfides of the protein can be reduced without dissociating the heavy and light chains. Furthermore, U.S. Patent No. 4,751,286 does not disclose attaching albumin to the IgG. The drug, label or dye is attached via a bridging structure within the IgG between two cysteines that are normally in a disulfide linkage with each other. The purpose of this approach is to retain the natural antibody structure. For example, U.S. Patent No. 4,751,286 discloses inserting crabescein below the hinge region. This region was chosen as there is little interchain interaction between heavy chains, unlike the region of the interchain disulfide bond in the Fab segment. Thus, there was sufficient space for crabescein to reside within the normal antibody structure (column 6, lines 62-67). The third disulfide bond was used for insertion of crabescein, the most distal from the Fab arms (column 7, line 1).

The Examiner asserts that the motivation for one skilled in the art to conjugate albumin to the antibody conjugate of U.S. Patent No. 4,751,286 would be to make the antibody more resistant to bioinactivation. However, there is no motivation in U.S. Patent No. 4,751,286 to do this. In fact, U.S. Patent No. 4,751,286 states that, due to the retention of the native form of the protein by use of the bridging structure (column 4, line 3), **"an antibody is likely to maintain its biological activity"**. The purpose of the bridging structure used in U.S. Patent No. 4,751,286 is to retain the natural conformation of the protein, to retain biological activity and to avoid immunogenicity issues arising from surface attachment of drugs or labels. Applicants assert that there is no motivation to attach albumin to these antibodies.

The Examiner asserts that it would have been obvious to conjugate albumin as disclosed in U.S. Patent No. 4,749,570 to the antibody conjugate disclosed in U.S. Patent No. 4,751,286. the antibody conjugate taught by U.S. Patent No. 4,751,286 is a whole IgG and the purpose of the bridging structure is to retain the internal disulfide bonds and to maintain the IgG structure. There are therefore no free cysteins in the IgG conjugate and attachment of albumin to only one cysteine in the hinge would disrupt the disulfide bond and hence the internal structure of the IgG. Applicants assert that there would be no motivation to do this as it would contradict the rationale of U.S. Patent No. 4,751,286, which is for retention of native structure.

Even if a skilled artisan had conjugated albumin to the conjugate of U.S. Patent No. 4,751,286, there is no motivation provided in U.S. 4,749,570 to maintain the native structure of the albumin carrier by non-disruption of intrachain disulfide bonds. U.S. 4,749,570 describes a process for chemical linkage of a therapeutic agent and a targeting agent to a carrier albumin which in most cases utilizes a cross-linking agent such as glutaraldehyde, sodium periodate and water soluble carbodiimide (column 3, line 47). There is no suggestion that bridging structures could be used or that it would be desirable to retain albumin in its native form. In fact, column 6, line 1 states that the conditions used for cross-linking should be such that the biological activity of the therapeutic agent and the binding specificity of the targeting agent are maintained. There is no mention of a need to maintain the native structure of the albumin. The conjugates produced were shown to be non-immunogenic demonstrating that there were no issues with the albumin or the cross-linking used that would motivate the person skilled in the art to seek alternatives.

In the absence of any motivation to use albumin in its native form or to look for alternative conjugation methods, the skilled artisan would have no motivation to look at the Peters reference or to single out the cysteine of position 34 as a site of attachment.

Furthermore, the skilled artisan would not have had any motivation to look at U.S. patent No. 6,350,431 in which albumin is only found in a long list of possible linkers. No explicit disclosure of the desired linker length of 10 to 20 angstroms can be found in U.S. 6,350,431, nor is there any disclosure that this length would be desirable to prevent unwanted albumin homodimer formation or to enable an antibody fragment to retain its full binding ability as disclosed in the present application.

Accordingly, Applicants assert that claims 14, 15 and 17-20 are not obvious in view of U.S. Patent No. 4,751,286 in view of U.S. patent No. 4,749,570, Peters IDS reference "AT" and the known facts disclosed in the specification on page 27, lines 9-13. Withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

Fees

A check in the amount of $110.00 for a one-month extension of time is enclosed. No other fees are believed to be necessitated by this response, but if any other fees are found to be required, the Commissioner is hereby authorized to charge any fees, or credit any overpayment, to Deposit Account No. 11-1153.

Conclusion

Applicants believe that the outstanding rejections based on 35 U.S.C. §112 and 35 U.S.C. § 103(a) have been overcome by the amendments presented above. Thus, reconsideration and withdrawal of the outstanding grounds of rejection, and early allowance of the claims as amended is believed to be in order and is courteously solicited.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned at the number listed below, so that prosecution of the application may be expedited.

Respectfully submitted,

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